tamoxifen, taxol, vinblastine, vincristine, indinavir, ritonavir, saquinavir, testosterone, prednisolone, methylprednisolone, dexamethasone, proguanil, warfarin, finasteride, flutamide, ondansteron, zatsetrone, cisapride, cortisol, zonisamide, desmethyldiazepam, and conivaptan.

REMARKS

Claims 1-17 are pending in this application and presented for examination. Claims 16 and 17 are newly added. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." In addition, for the Examiner's convenience, the pending claims are set forth in the Appendix. Reconsideration is respectfully requested.

I. THE INVENTION

The present invention provides, *inter alia,* systems and methods for averting undesirable pharmacokinetic drug interaction between a drug and a concomitant drug(s) by controlling *in vivo* release time and/or the release site of the drug and/or the concomitant drug.

The present invention is based upon the surprising discovery that with respect to drug interaction, which is produced as a result of the drugs themselves competing for one route (for example, enzyme, carrier, *etc.*) with multiple drugs that use the same route in terms of drug absorption, distribution, metabolism or excretion, drug interaction at the route can be averted by controlling the drug release time and/or release site with a drug delivery system. Advantageously, the systems and methods of the present invention are not only effective with regard to drug interaction between multiple drugs, but also interaction between drugs and foods.

II. SUPPORT FOR THE NEW CLAIMS

Support for new claims 16 and 17 is found throughout the application as filed. More particularly, support for claim 16 is found, for example, in claims 8-9. Support for claim 17 is found, for example, in claims 7-9. As such, no new matter has been added and Applicants respectfully request that the Examiner enter the claims.

III. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-15 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,891,223 ("Ambegaonkar *et al.*"). The Examiner, acknowledges that Ambegaonkar *et al.* do not disclose that the formulation averts an undesirable pharmacokinetic interaction. However, the Office Action alleges that since a controlled released drug slowly releases the drug into the system it may ***inherently*** avert undesirable pharmacokinetic drug interaction between the drug and concomitant drug. In response, Applicants respectfully traverse the rejection.

A. Obviousness cannot be predicated on what is unknown.

The Examiner is respectfully reminded that it is improper to rely upon inherent properties in an obviousness rejection unless the inherent properties would themselves be entirely explicit to one of skill upon viewing the reference. (*see, S Kloster AB v. Crusible Inc.*, 793 F.2d 1565 (Fed. Cir. 1986)). As stated by the CCPA:

> The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessary known. Obviousness cannot be predicated on what is unknown. *In re Shetty*, 566 F.2d 81, 195 USPQ 753, 757 (CCPA 1977).

Ambegaonkar *et al.* relate to a coating formulation for a bioactive substance that results in a first-order, fractional-order, zero-order, or biphasic release of the bioactive substance (*see*, column 1, lines 6-11, Ambegaonkar *et al.*). More particularly, Ambegaonkar *et al.* relate to a bioactive composition having a controlled, sustained release delivery pattern when contacted with a suitable surrounding media comprising (a) a bioactive material core, (b) a first coating enveloping the bioactive material core, and (c) a second coating enveloping the first coating, whereby when the composition is exposed to the surrounding media, the exposure will result in the controlled release of the bioactive material (*see*, column 19, lines 37, and column 20, line 12, Ambegaonkar *et al.*).

Contrary to the teaching of Ambegaonkar *et al.*, the present invention pertains to a novel and unobvious means for averting undesirable pharmacokinetic (drug) interaction between a drug and concomitant drug(s) (*e.g.*, between a drug and a food) *in vivo* in humans (*see*, page 1, lines 8-11 of the specification). As the means of averting such undesirable drug interactions, the

present invention provides a drug delivery system that controls *in vivo* release time and/or the release site of the drug. Ambegaonkar *et al.* do ***not*** teach ***implicitly, inherently or explicitly***, anything about averting undesirable pharmacokinetic (drug) interaction. In fact, use of the controlled release compositions of Ambegaonkar *et al.* could result in an adverse drug interaction if two drugs are released at the same rate and administered at the same time. There is ***no*** teaching in Ambegaonkar *et al.* to avert the undesirable pharmacokinetic (drug) interaction between a drug and concomitant drugs(s).

Obviousness cannot be predicated on something that is unknown. Applicants assert that it is improper to rely upon inherent properties in an obviousness rejection unless the inherent properties would themselves be entirely explicit to one of skill upon viewing the reference. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

B. The is no Teaching or Suggestion to Modify the Reference.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As stated above, Ambegaonkar *et al.* relate to a coating formulation for a bioactive substance that results in a first-order, fractional-order, zero-order, or biphasic release of the bioactive substance (*see*, column 1, lines 6-11, Ambegaonkar *et al.*). More particularly, Ambegaonkar *et al.* relate to a bioactive composition having a controlled, sustained release delivery pattern when contacted with a suitable surrounding media comprising (a) a bioactive material core, (b) a first coating enveloping the bioactive material core, and (c) a second coating enveloping the first coating, whereby when the composition is exposed to the surrounding media, the exposure will result in the controlled release of the bioactive material (*see*, column 19, lines 37, and column 20, line 12, Ambegaonkar *et al.*).

Contrary to the teaching of Ambegaonkar *et al.*, the present invention pertains to a novel means for averting undesirable pharmacokinetic (drug) interaction between a drug and

concomitant drug(s) (*e.g.*, between a drug and a food) *in vivo* in humans (*see*, page 1, lines 8-11 of the specification). As the means of averting such undesirable drug interactions, the present invention provides a drug delivery system that controls the *in vivo* release time and/or the release site of the drug. At ***no*** point do Ambegaonkar *et al.* teach anything about a system to avert undesirable pharmacokinetic (drug) interaction. There is ***no*** teaching in Ambegaonkar *et al.* to avert the undesirable pharmacokinetic (drug) interaction between a drug and concomitant drugs(s).

In view of Ambegaonkar *et al.*, there is simply no motivation for one of ordinary skill in the art to avert drug interaction by controlling the drug release time and/or release site with drug delivery systems and methods as is presently taught and claimed. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

C. The Cited Art Does Not Teach All the Claim Limitations

The cited art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants assert that the cited art reference does not teach or suggest all the limitations of the claims and therefore, the obviousness rejection in untenable.

Ambegaonkar *et al.* provide controlled, sustained release, particularly zero-order release compositions, which causes a drug to be released at a uniform rate. The systems of Ambegaonkar *et al.* are limited, however, because they ***cannot*** avert the undesirable pharmacokinetic (drug) interaction between a drug and concomitant drugs(s). In fact, using the controlled release compositions of Ambegaonkar *et al.* could result in an adverse drug interaction if both two drugs are released at the same rate and administered at the same time. There is ***no*** teaching in Ambegaonkar et al. to avert the undesirable pharmacokinetic (drug) interaction between a drug and concomitant drugs(s) as is presently taught and claimed.

The present invention, which relates to systems and methods for averting undesirable pharmacokinetic drug interaction between a drug and concomitant drug(s), by controlling the *in vivo* release time and/or release site of the drug and/or the concomitant drug, is not obvious in view of Ambegaonkar *et al.* Again, Ambegaonkar *et al.* do not teach or suggest

averting the undesirable pharmacokinetic (drug) interaction between a drug and concomitant drug as is presently taught and claimed. Under *In re Wilson supra*, a *prima facie* case of obviousness has not been established because each of the limitation of the claims is not taught or suggested in the cited art reference.

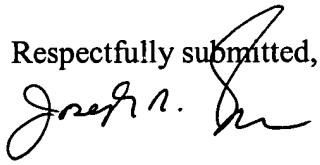
Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

IV. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The following new claims have been added:

16. (New) A drug preparation for averting undesirable effects on the blood concentration of a drug by concomitant drug(s) that inhibits the *in vivo* metabolism of the said drug by CYP3A4 in humans, which comprises timed release control of the said drug or controlling release specifically in the lower digestive tract of the concomitant drug, whereby:

the said drug and the concomitant drug are a combination selected from anfentanyl, fentanyl, sulfentanyl, cocaine, dihydrocodeine, oxycodeine, tramadol, erythromycin, clarithromycin, troleandomycin, azithromycin, itraconazole, ketoconazole, dapsone, midazolam, triazolam, alprazolam, diazepam, zolpidem, felodipine, nifedipine, nitrendipine, amlodipine, isradipine, nicardipine, nimodipine, nisoldipine, nildipine, bepridil, diltiazem, verapamil, astemizole, terfenadine, loratidine, cyclosporine, tacrolimus, rapamycin, amiodarone, disopyramide, lidocaine, propafenone, quinidine, imipramine, amitriptyline, clomipramine, nafazodone, sertraline, trazodone, haloperidol, pimozide, carbamazepine, ethosuximide, trimethadione, simvastatin, lovastatin, fluvastatin, atrovastatin, etoposide, ifosfamide, paclitaxel, tamoxifen, taxol, vinblastine, vincristine, indinavir, ritonavir, saquinavir, testosterone, prednisolone, methylprednisolone, dexamethasone, proguanil, warfarin, finasteride, flutamide, ondansteron, zatsetrone, cisapride, cortisol, zonisamide, desmethyldiazepam, and conivaptan.

17. (New) A drug preparation for averting undesirable drug interaction on the *in vivo* kinetics of a drug by concomitant drug(s) that inhibits *in vivo* metabolism of the said drug in humans, which comprises timed-release control of the concomitant drug or control of the site of release of the concomitant drug to the digestive tract whereby:

the said drug and the concomitant drug are a combination selected from anfentanyl, fentanyl, sulfentanyl, cocaine, dihydrocodeine, oxycodeine, tramadol, erythromycin, clarithromycin, troleandomycin, azithromycin, itraconazole, ketoconazole, dapsone, midazolam, triazolam, alprazolam, diazepam, zolpidem, felodipine, nifedipine, nitrendipine, amlodipine, isradipine, nicardipine, nimodipine, nisoldipine, nildipine, bepridil, diltiazem, verapamil, astemizole, terfenadine, loratidine, cyclosporine, tacrolimus, rapamycin, amiodarone, disopyramide, lidocaine, propafenone, quinidine, imipramine, amitriptyline, clomipramine,

nafazodone, sertraline, trazodone, haloperidol, pimozide, carbamazepine, ethosuximide, trimethadione, simvastatin, lovastatin, fluvastatin, atrovastatin, etoposide, ifosfamide, paclitaxel, tamoxifen, taxol, vinblastine, vincristine, indinavir, ritonavir, saquinavir, testosterone, prednisolone, methylprednisolone, dexamethasone, proguanil, warfarin, finasteride, flutamide, ondansteron, zatsetrone, cisapride, cortisol, zonisamide, desmethyldiazepam, and conivaptan.